



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB00/00469 (22) International Filing Date: 11 February 2000 (11.02.00) (30) Priority Data: 9903784.8          18 February 1999 (18.02.99)          GB (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY LIMITED [GB/GB]; Kingsclere Road, Basingstoke, Hampshire RG21 6XA (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): FAIRHURST, John [GB/GB]; 17 Hinton Fields, Kings Worthy, Winchester, Hampshire SO23 7QB (GB). (74) Agent: HUDSON, Christopher, Mark; Eli Lilly and Company Limited, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report.	
(54) Title: 1-((INDOLYL AZACYCLOALKYL) ALKYL)-2,1, 3-BENZOTHIADIAZOLE 2,2-DIOXIDES EXHIBITING 5-HT <sub>2A</sub> RECEPTOR ACTIVITY			
<div style="text-align: right;">(I)</div>			
(57) Abstract  A pharmaceutical compound of (I) in which m is 0, 1 or 2, n is 1 or 2, p is 1 or 2, q is 1 to 6, r is 0 or 1 to 3, R <sup>1</sup> is halo, C <sub>1-4</sub> alkyl, nitrile, trifluoromethyl or C <sub>1-4</sub> alkoxy, R <sup>2</sup> and R <sup>3</sup> are each hydrogen or C <sub>1-4</sub> alkyl, R <sup>4</sup> is hydrogen, C <sub>1-4</sub> alkyl, optionally substituted phenyl or optionally substituted phenyl-C <sub>1-4</sub> alkyl, R <sup>5</sup> is C <sub>1-4</sub> alkyl, C <sub>1-4</sub> alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, nitro or amino, and the dotted line represents an optional double bond; and salts and esters thereof.			

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1-((INDOLYL AZACYCLOALKYL) ALKYL)-2,1, 3-BENZOTHIADIAZOLE 2,2-DIOXIDES EXHIBITING 5-HT<sub>2A</sub> RECEPTOR ACTIVITY

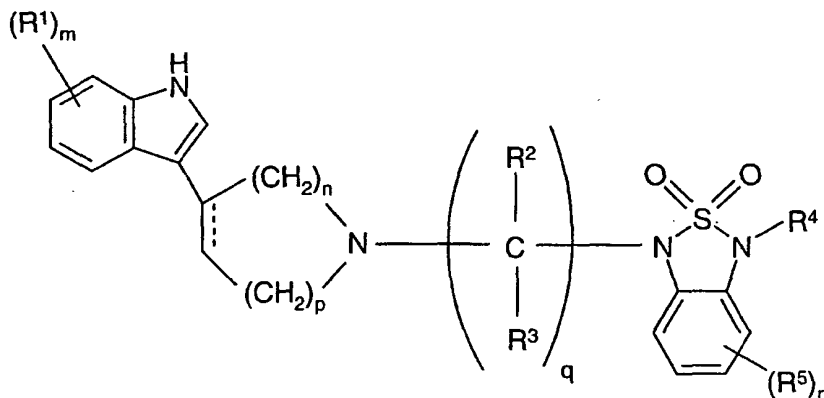
This invention relates to novel compounds with pharmaceutical properties.

5

It is well known that compounds active at serotonin receptors have potential in the treatment of disorders of the central nervous system and, for example, certain halo-substituted indole compounds having serotonin antagonist properties are disclosed in EP-A 0433149 and WO 98/31686.

The compounds of the invention are of the following formula:

15



(I)

in which m is 0, 1 or 2, n is 1 or 2, p is 1 or 2,

q is 1 to 6, r is 0 or 1 to 3,

R<sup>1</sup> is halo, C<sub>1-4</sub> alkyl, nitrile, trifluoromethyl or C<sub>1-4</sub>  
5 alkoxy,

R<sup>2</sup> and R<sup>3</sup> are each hydrogen or C<sub>1-4</sub> alkyl,

R<sup>4</sup> is hydrogen, C<sub>1-4</sub> alkyl, optionally substituted  
10 phenyl or optionally substituted phenyl-C<sub>1-4</sub> alkyl,

R<sup>5</sup> is C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, hydroxy, cyano,  
halo, trifluoromethyl, nitro or amino, and

15 the dotted line represents an optional double bond;

and salts and esters thereof.

The compounds of the invention and their  
20 pharmaceutically acceptable salts and esters are  
indicated for use in the treatment of disorders of the  
central nervous system.

A C<sub>1-4</sub> alkyl group can be methyl, ethyl or propyl and  
25 can be branched or unbranched and includes isopropyl and

tert. butyl. A C<sub>1-4</sub> alkoxy group is one such C<sub>1-4</sub> alkyl group attached through oxygen to the ring. An optionally substituted phenyl-C<sub>1-4</sub> alkyl group is an optionally substituted phenyl attached through one such C<sub>1-4</sub> alkyl group, and is preferably optionally substituted phenyl-(CH<sub>2</sub>)<sub>x</sub>- where x is 1 or 2, and most preferably optionally substituted benzyl. A halo substituent is preferably fluoro, chloro or bromo.

10 An optionally substituted phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, for example C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, nitro and amino.

15

It will be appreciated that when m is 2 the values of R<sup>1</sup> need not be the same, when p is more than one, the recurring unit is not necessarily the same, and when r is 2 or 3 the values of R<sup>5</sup> need not be the same.

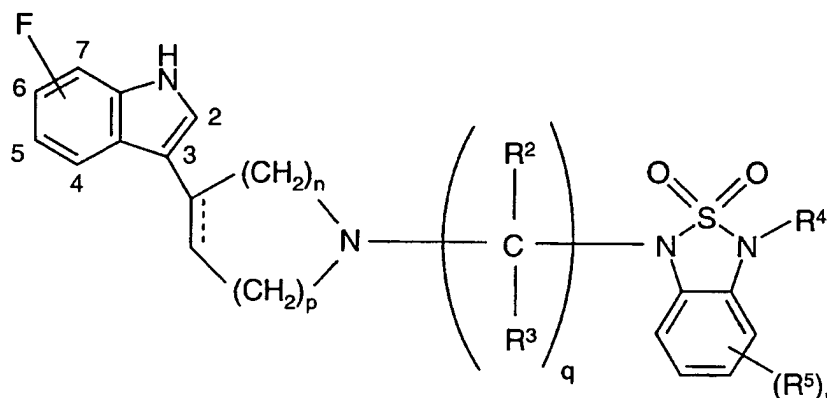
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A preferred group of compounds is one of formula (I) above, in which the dotted line represents a double bond, n is 2, m is 1 or 2, and p is 1, R<sup>2</sup> and R<sup>3</sup> are both hydrogen, q is 2, R<sup>3</sup> is C<sub>1-4</sub> alkyl, and r is 0 or

1. When  $R^1$  is  $C_{1-4}$  alkyl or  $C_{1-4}$  alkoxy it is preferably methyl or methoxy, respectively.

Substituent  $(R^1)_m$  preferably represents 6-fluoro,  
 5 7-fluoro, 6,7-difluoro, or 6-fluoro-7-methyl.

Preferred compounds are those of the following formula (II):



(II)

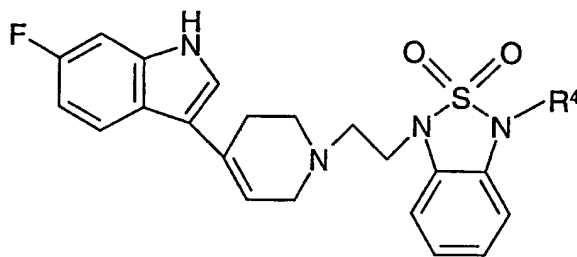
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and preferred sub-groups exhibit one or more of the following features:

- 15 (i) the fluorine substituent is in the 6- or 7-position, and preferably in the 6-position
- (ii) the dotted line represents a double bond
- (iii)  $n$  is 2 and  $p$  is 1

- (iv)  $R^2$  and  $R^3$  are both hydrogen
- (v)  $q$  is 2
- (vi)  $R^4$  is  $C_{1-4}$  alkyl, especially isopropyl
- (vii)  $r$  is 0 or 1, and preferably 0 (unsubstituted)
- 5 (viii)  $R^5$  is  $C_{1-4}$  alkoxy, hydroxy, halo or amino ( $-NH_2$ ).

A particularly preferred group of compounds is of the formula:



(III)

10

in which  $R^4$  is  $C_{1-4}$  alkyl and especially isopropyl, or a pharmaceutically acceptable salt thereof.

- 15 As indicated above, it is, of course, possible to prepare salts of the compound of the invention and such salts are included in the invention. Acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as
- 20 those with inorganic acids, for example hydrochloric,

hydrobromic, nitric, sulphuric or phosphoric acids, or  
with organic acids, such as organic carboxylic acids,  
for example, glycollic, maleic, hydroxymaleic, fumaric,  
malic, tartaric, citric, salicylic, o-acetoxybenzoic,  
5 or organic sulphonic, 2-hydroxyethane sulphonic,  
toluene-p-sulphonic, or naphthalene-2-sulphonic acid.

In addition to the pharmaceutically acceptable salts,  
other salts are included in the invention. They may  
10 serve as intermediates in the purification of compounds  
or in the preparation of other, for example  
pharmaceutically acceptable, acid addition salts, or are  
useful for identification, characterisation or  
purification.

15

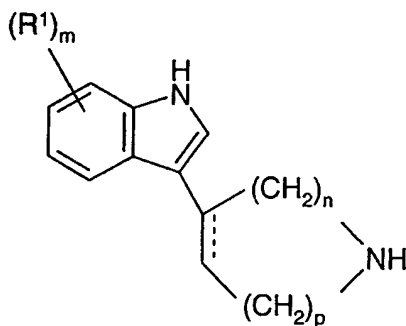
It will be appreciated that when a phenyl substituent is  
acidic such as, for example, a carboxy group, the  
opportunity exists for esters. These can be aliphatic  
or aromatic, being preferably alkyl esters derived from  
20 C<sub>1-4</sub> alkanols, especially methyl and ethyl esters. An  
example of an ester substituent is -COOR' where R' is  
C<sub>1-4</sub> alkyl.

Some of the compounds of the invention contain one or  
25 more asymmetric carbon atoms which gives rise to  
isomers. These compounds are normally prepared as



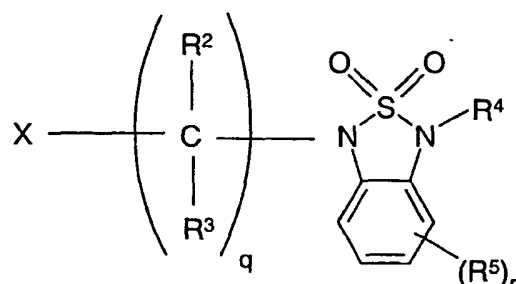
racemic mixtures and can conveniently be used as such,  
but individual isomers can be isolated by conventional  
techniques, if so desired. Such racemic mixtures and  
individual optical isomers form part of the present  
5 invention. It is preferred to use an enantiomerically  
pure form.

The invention also includes a process for producing a  
compound of formula (I) above, which comprises reacting  
10 a compound of the formula:



(IV)

with a compound of the formula:



(V)

where the substituents have the values given above, and  
 X is a leaving group such as, for example, a halo atom,  
 5 or a mesylate or tosylate.

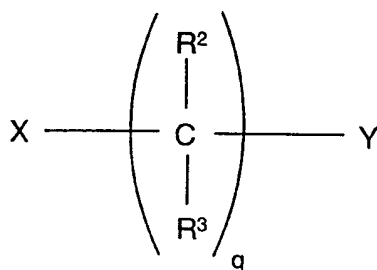
The reaction is preferably carried out in a polar  
 solvent such as, for example, acetonitrile or water, at  
 a temperature of from 50° C. to 150° C., and in the  
 10 presence of sodium iodide and a base such as, for  
 example, sodium carbonate

The coupling can also be effected by reacting the  
 compound of formula (IV) with an aldehyde equivalent of  
 15 the compound of formula (V). Such aldehydes can be  
 prepared from the appropriate terminal alkene by  
 oxidation employing, for example, ozone or osmium  
 tetroxide, followed by reductive amination using, for  
 example, sodium cyanoborohydride, borane in pyridine or  
 20 sodium triacetoxy borohydride, and the compound of

formula (IV). This reaction is preferably carried out at a temperature of from -20° C. to 50° C., in a solvent such as, for example, dichloromethane.

- 5 The intermediate compounds of formula (IV) are known in the art, and compounds of formula (V) can be prepared by preparative routes as follows. For example, compounds of formula (V) can be prepared by reacting the appropriate alkane derivative of formula:

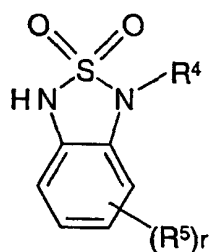
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(VI)

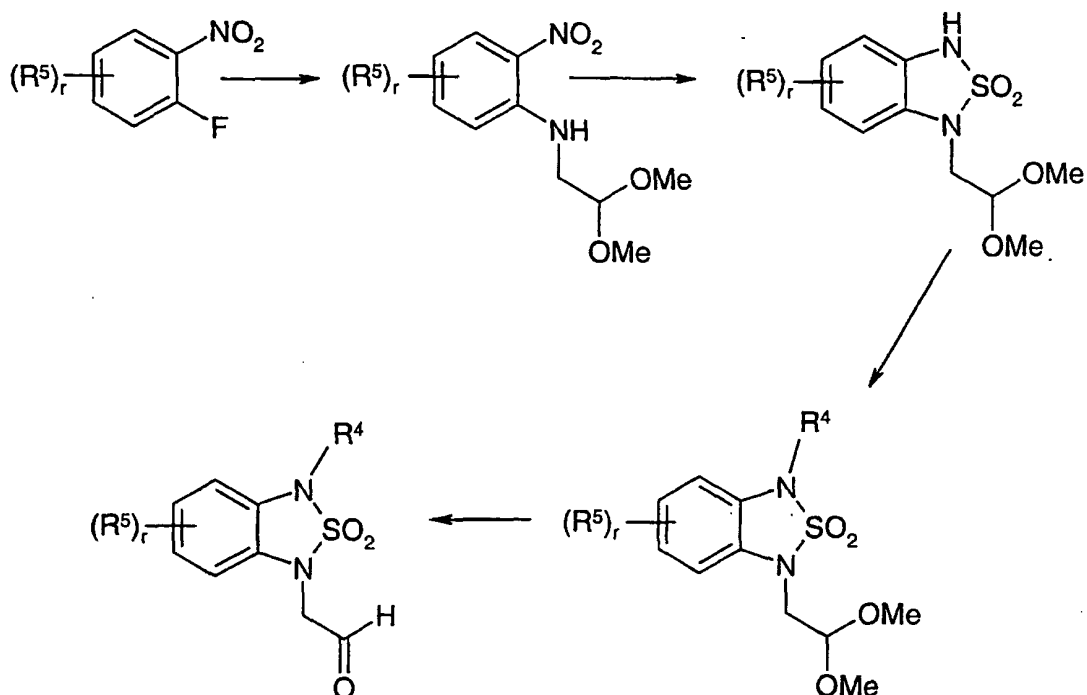
where X is a leaving group, and Y is halo, preferably bromo, with a compound of formula:

15



(VII)

- Preferred alkane reactants are dihalo-alkanes, for instance bromo chloroethane, and the reaction is
- 5 preferably carried out in an organic solvent such as, for example, dimethylformamide, with a strong base such as sodium hydride, at a temperature of from 0° C. to 100° C., for instance at room temperature.
- 10 Compounds of formula (VII) above can be prepared, for example, as follows:



As mentioned above, the compounds of the invention and  
 5 their pharmaceutically acceptable salts have useful  
 central nervous system activity. The compounds are  
 active at the serotonin, 5-HT<sub>2A</sub>, receptor. Their  
 binding activity has been demonstrated in a test  
 described by Nelson, D. L. et al, J. Pharmacol. Exp.  
 10 Ther., 265, 1272-1279, in which the affinity of the  
 compound for the human 2A receptor is measured by its  
 ability to displace the ligand [<sup>3</sup>H] ketanserine. In  
 this test, the compounds of the invention in the  
 following Examples had a K<sub>i</sub> of less than 15 nM. The  
 15 compounds of the invention are also active serotonin

reuptake inhibitors as measured by their displacement of [3H] paroxetine at the reuptake site, Neuropharmacology Vol. 32 No. 8, 1993, pages 737-743.

5 Because of their selective affinity for 5-HT receptors, the compounds of the present invention are indicated for use in treating a variety of conditions such as depression, obesity, bulimia, alcoholism, pain, hypertension, ageing, memory loss, sexual dysfunction,  
10 anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's and sleep disorders.

The compounds of the invention are effective over a wide  
15 dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage required will normally fall within the range of 0.01 to  
20 20 mg/kg per day, for example in the treatment of adult humans, dosages of from 0.5 to 100 mg per day may be used.

The compounds of the invention will normally be  
25 administered orally or by injection and, for this purpose, the compounds will usually be utilised in the

form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

5

Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, associated with a pharmaceutically acceptable excipient. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. The excipient may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

25

Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions or suspensions for parenteral use or as suppositories.

- 5 Preferably the compositions are formulated in a dosage unit form, each dosage containing from 0.5 to 100 mg, more usually 1 to 100 mg, of the active ingredient.

The following Preparations and Examples illustrate  
10 routes to the synthesis of the compounds of the invention.

#### PREPARATION 1

15 6-Fluoroindole

1-Dimethylamino-2-(4-fluoro-2-nitro)phenylethene

- A mixture of 4-fluoro-2-nitrotoluene (50 g, 0.32 mol), dimethylformamide dimethylacetal (76.77 g) and dimethylformamide (910 ml) were  
20 heated under reflux under nitrogen with stirring for 7 hours, cooled, allowed to stand for 16 hours, poured into ice-water (2000 ml), stirred for 15 minutes and the resultant precipitate isolated by filtration, washed with water (500 ml), dried to  
25 give a red solid.



6-Fluoroindole

A 40 litre Cook hydrogenator was charged under a nitrogen atmosphere with 10% palladium on charcoal (9 g) suspended in toluene (400 ml). To this suspension was added 1-dimethylamino-2-(4-fluoro-2-nitro)phenylethene (137.2 g, 0.653 mol) in toluene (1400 ml) and the mixture hydrogenated at 80 psi for 3.5 hours. The suspension was then filtered through a celite pad, which was washed through with toluene (2 x 200 ml) and the filtrate and washings evaporated under reduced pressure to give a brown oil which crystallised on standing to a yellow brown solid 93.65 g. This solid was dissolved in ethyl acetate-hexane (7:3) and filtered through a pad of flash silica. The required fractions were collected and evaporated under reduced pressure to give a pale brown solid.

20 PREPARATION 24-(6-Fluoroindol-3-yl)-1,2,5,6-tetrahydropyridine

Powdered potassium hydroxide (144.4 g) was added carefully to a mechanically stirred mixture of 6-fluoroindole (49.23 g, 0.364 mol) and

- 16 -

4-piperidone monohydrate (111.93 g, 0.728 mol) in methanol (1500 ml). The mixture was then heated under reflux under nitrogen for 18 hours and then more potassium hydroxide (40 g) was added and the reaction mixture heated under reflux for a further 4 hours. The reaction mixture was allowed to cool to room temperature and poured onto ice-water (3000 ml) and stirred for 1 hour and the precipitated solid isolated by filtration and dried at 50° C. in vacuo to give a solid.

EXAMPLE 1

1-{2-[4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3-methyl-1,3-dihydro-2,1,3-benzothiadiazole-2,2-dioxide

To a 250 ml 3-necked round bottom flask equipped with reflux condenser, thermometer, magnetic stirrer bar and nitrogen bubbler was charged with sulphamide (9.61 g; 0.1 mol) and pyridine (100 ml) and the stirred solution heated to reflux under nitrogen. N-methyl-1,2-phenylene diamine (12.2 g, 0.1 mol) in dry pyridine (30 ml) was added dropwise to the solution whilst maintaining reflux. After 5 hours, the reaction mixture allowed to

cool and the pyridine removed under reduced pressure.

The residue was dissolved in 5N hydrochloric acid (100 ml) and ethyl acetate (100 ml) and the acidic layer was extracted with further ethyl acetate (5 x 100 ml).

5 The combined organic layer was washed with 5N hydrochloric acid (2 x 100 ml), extracted with 2N sodium hydroxide solution (3 x 100 ml) and the combined aqueous layer washed with diethyl ether (2 x 150 ml). Ice was then added followed by the addition of 5N hydrochloric  
10 acid with cooling and stirring of the suspension to pH 1. The oily suspension was stirred for several hours at room temperature when a colourless solid separated. The solid was filtered and dried at room temperature under vacuum to leave a light pink solid, 1,3-dihydro-1-  
15 methyl-2,1,3-benzothiadiazole-2,2-dioxide, which was used directly in the next step.

1,3-dihydro-1-methyl-2,1,3-benzothiadiazole-2,2-dioxide (1.36 g, 7.4 mmol) was dissolved in DMF (40 ml) and then  
20 treated with sodium hydride (0.33 g, 60% oil dispersion, 8.2 mmol, 1.1 equivalent). The mixture was stirred at room temperature and under nitrogen for 45 minutes. 1-Bromo-2-chloroethane (0.74 ml, 1.27 g, 8.9 mmol, 1.2 equivalent) was added in one portion to the stirred  
25 mixture, and stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue suspended

in water and extracted into ethyl acetate (3 x 40 ml). The bulk extracts were washed with water (3 x 50 ml) and brine, then dried over anhydrous magnesium sulfate. Filtration was followed by evaporation to dryness  
5 in vacuo and the residue chromatographed on silica using dichloromethane as eluent. This gave a white solid [1-(2-chloroethyl)-1,3-dihydro-3-methyl-1H-2,1,3-benzothiadiazole-2,2-dioxide].

10 A mixture of 4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydropyridine (0.87 g, 4.0 mmol, 1.05 equivalent), 1-(2-chloroethyl)-1,3-dihydro-3-methyl-1H-2,1,3-benzothiadiazole-2,2-dioxide (1.1 g, 4.46 mmol), anhydrous sodium carbonate (2.34 g, 22.3 mmol, 5  
15 equivalents), sodium iodide (0.67 g; 4.46 mmol) and de-ionised water (20 ml) was rapidly stirred and warmed under reflux for 20 hours. After cooling to room temperature, the mixture was extracted with chloroform (3 x 30 ml). The bulked extracts were washed with water  
20 and then dried over magnesium sulfate. Filtration was followed by evaporation to dryness in vacuo to yield an orange solid. This material was purified further by chromatography on silica using dichloromethane initially followed by ethyl acetate to give the final product as  
25 an orange solid which was triturated with a mixture of diethyl ether and ethyl acetate. This gave a yellow

solid after filtration, 1-{2-[4-(6-fluoroindol-3-yl)-  
1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3-methyl-1,3-  
dihydro-2,1,3-benzothiadiazole-2,2-dioxide.

- 5 The compound was converted into its hydrochloride salt  
using ethereal HCl in ethanol with M.P. 246-8° C.

The following Examples illustrate typical formulations  
10 containing the compound of the invention.

EXAMPLE 2

Tablets each containing 10 mg of active ingredient are  
15 made up as follows:

	Active ingredient	10 mg
	Starch	160 mg
	Microcrystalline cellulose	100 mg
	Polyvinylpyrrolidone (as 10% solution in water)	13 mg
20	Sodium carboxymethyl starch	14 mg
	Magnesium stearate	3 mg
		_____
	Total	300 mg
		_____

- 20 -

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed  
5 through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

10 EXAMPLE 3

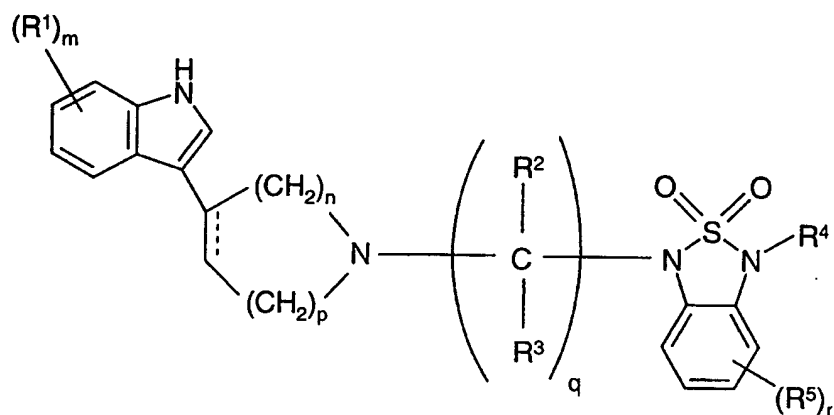
Capsules each containing 20 mg of medicament are made as follows:

15	Active ingredient	20 mg
	Dried starch	178 mg
	Magnesium stearate	2 mg
		_____
	Total	200 mg
20		_____

The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatine capsules in 200 mg quantities.

CLAIMS

1. A compound of the following formula:



in which  $m$  is 0, 1 or 2,  $n$  is 1 or 2,  $p$  is 1 or 2,

$q$  is 1 to 6,  $r$  is 0 or 1 to 3,

$R^1$  is halo,  $C_{1-4}$  alkyl, nitrile, trifluoromethyl or  $C_{1-4}$  alkoxy,

$R^2$  and  $R^3$  are each hydrogen or  $C_{1-4}$  alkyl,

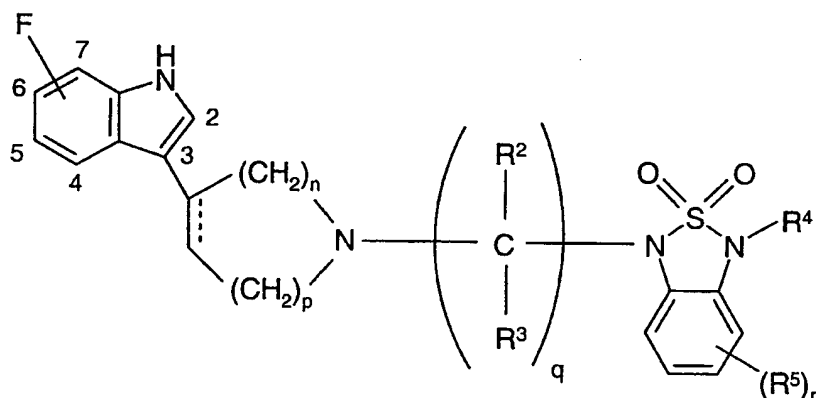
$R^4$  is hydrogen,  $C_{1-4}$  alkyl, optionally substituted phenyl or optionally substituted phenyl- $C_{1-4}$  alkyl,

$R^5$  is  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, nitro or amino, and

the dotted line represents an optional double bond;

and salts and esters thereof.

2. A compound according to Claim 1 of the formula:



in which  $n$  is 1 or 2,  $p$  is 1 or 2,

$q$  is 1 to 6,  $r$  is 0 or 1 to 3,

$R^2$  and  $R^3$  are each hydrogen or  $C_{1-4}$  alkyl,

$R^4$  is hydrogen,  $C_{1-4}$  alkyl, optionally substituted phenyl or optionally substituted phenyl- $C_{1-4}$  alkyl,



$R^5$  is  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, nitro or amino,

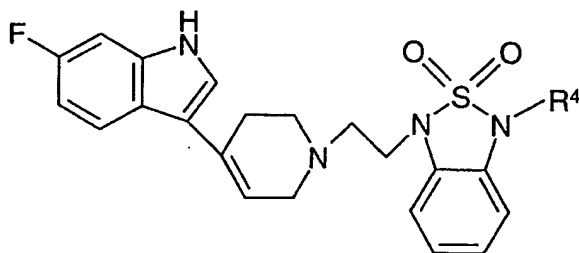
the dotted line represents an optional bond, and

the fluorine atom is attached at the 6 or 7-position;

or a salt or ester thereof.

3. A compound according to Claim 2, in which the dotted line represents a double bond,  $n$  is 2 and  $p$  is 1,  $R^2$  and  $R^3$  are both hydrogen,  $q$  is 2,  $R^4$  is  $C_{1-4}$  alkyl, and  $r$  is 0 or 1.

4. A compound according to Claim 2 of the formula:



in which  $R^4$  is  $C_{1-4}$  alkyl.

5. A pharmaceutical formulation comprising a compound  
as defined in any of Claims 2 to 4, or a  
pharmaceutically acceptable salt or ester thereof,  
5 together with a pharmaceutically acceptable diluent  
or carrier therefor.
6. A compound according to Claim 1, or a  
pharmaceutically acceptable salt or ester thereof,  
10 for use as a pharmaceutical.
7. Use of a compound according to any of Claims 1 to  
4, or a pharmaceutically acceptable salt or ester  
thereof, in the manufacture of a medicament for use  
15 in the treatment of a disorder of the central  
nervous system.

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/GB 00/00469

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/14 A61K31/41 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

28 April 2000

Date of mailing of the international search report

09/05/2000

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